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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,592	07/13/2001	Keiya Ozawa	50026/012003	6387

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,592	OZAWA ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6,8,10,12,14,15 and 17-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *14 and 18* is/are allowed.

6)☒ Claim(s) *5,6,8,10,12,15,17 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 07 November 2005, amending claims 5, 8, 14, 15 and adding new claims 20-24. Claims 5-6, 8, 10, 12, 14-15 and 17-24 are pending in this application.

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. As no new grounds of rejection are set forth, **this action is made FINAL**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 5-6, 8, 10, 12, 14-15 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This rejection is of record and is repeated herein in salient part. A response to Applicant's arguments is set forth immediately following the body of the rejection. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the

application was filed, had possession of the claimed invention. More particularly, the claims are directed to a genus of nucleic acid structures (i.e., vector molecules) encoding fusion proteins comprising deletion of *any portion* of the G-CSFR extra-cellular domain where said truncated G-CSFR must correspond to proliferation activity. As such, the claim is directed to a genus of nucleic acids that encode an amino acid sequence wherein *any* portion encoding any amino acid residue(s) is deleted. Thus even where the cytokine receptor is delimited to G-CSF, the claim is still drawn to a genus of structures – deletions in *any portion* the extracellular domain – with the prescribed function of inducing cell proliferation.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus. Furthermore, the Guidelines for Written Description state (hereinafter Guidelines):

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

The specification does not provide sufficient description for a representative number of structural properties coupled with a known or disclosed structure to function correlation. The

specification discloses an example of Ba/F3 or murine mononuclear cells transformed with three variants of one type of cytokine receptor proliferation domain (i.e., murine G-CSF receptor). More particularly, two relevant fusion constructs are disclosed comprising a chimeric G-CSF receptor/estrogen ligand binding domain construct – "GCRER", as well as a construct with portions deleted in the G-CSFR extracellular domain from the 5th to the 195th residue – GCRΔ (5-195)/ER. (e.g., p. 9, Example 1). Therefore, GCRΔ (5-195)/ER and GCRER are the only relevant embodiments that are disclosed. **Thus out of the potential thousands of species encompassed by the genus of deletions (i.e., combinations/permutations of deletions in the G-CSFR extracellular domain), the disclosure provides a single species.**

In sum, two embodiments of a cytokine receptor are disclosed and one embodiment for a hormone ligand-binding domain (HBD), linked to either the wild type G-CSFR or GCRΔ (5-195). No further structures are disclosed where *any* portion of the G-CSFR extracellular domain is deleted in the context of a fusion molecule imparting cell proliferation or where any other HBD is linked to any other cytokine receptor. Further, notwithstanding the boundaries of the extracellular domain for murine G-CSFR, there are hundreds to thousands of potential deletions or combinations of deletions that read on claim 5, where each structure must correlate to the function of imparting proliferation activity. In sum, the lack of disclosure of a sufficient number of embodiments of said fusion proteins results in a description gap in the instant disclosure.

The knowledge in the art does not provide sufficient relevant information to fill the gap present in the instant disclosure. For example, there are a few examples of particular fusion molecules consisting of a cytokine receptor and a hormone ligand-binding domain, whereby the fusion protein imparts cell proliferation. (e.g., *Capon et al.* US 5,837,544; teaching a chimeric

constructs encoding a ligand-binding domain or an inducer-responsive clustering domain (ICD) linked to a proliferation signaling domain (PSD); *Nakabeppu et al.* Mol. Cell. Biol. 1993; 13:4157-66; teaching a fusion protein comprising the *FosB* cytokine receptor domain linked to the human estrogen receptor ligand binding domain, whereby *FosB* regulated proliferation of quiescent cells).

However, a handful of examples do not suffice to describe the genus of fusion molecule structures encompassed by the claims, wherein said structures correlate to cell proliferation. The fusion molecule components (i.e., cytokine receptor domains and hormone ligand binding domains) are the essential element of the invention, but are not shown to be necessarily interchangeable, so that any combination will not necessarily result in the function of imparting cell proliferation. Such fusion constructs are not deemed to be "conventional" in the art, in the context of cell proliferation. (Supra, Guidelines, discussing critical or essential features of a claimed genus and the relative need for description when a feature is conventional in the art).

In sum, given the enormous breadth of the genus of fusion molecules encompassed by the rejected claims, and given the limited description from the instant specification of such fusion molecules, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species (i.e., different combinations of receptors/binding domains comprising a given fusion molecule). Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. In reviewing the entirety of Applicant's Remarks, it does not appear that Applicant asserts any specific arguments regarding the genus of nucleic acid molecules encompassing *deletions in the G-CSFR extracellular domain*. Applicant asserts the following that appear to be relevant to the instant rejection: (1) Applicant merely asserts that by comparing amino acid sequences that one of skill would recognize whether an extracellular domain contains a deletion. (Remarks, p. 11, middle ¶); (2) More generally, Applicant asserts that there is no requirement to describe a representative number of species, or to describe every species. (e.g., Remarks, p. 12, ¶ 2); and (3) Applicant asserts that routine screening can identify inoperable fusion proteins and that any experimentation needed to practice the invention is not undue. (e.g., Remarks, p. 13).

As to Applicant's last assertion, it is respectfully pointed out that the argument is probative only for an enablement rejection, for which the basis of rejection is entirely distinct from that for a written description rejection. The written description requirement is separate and distinct from the enablement requirement. *See In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.) Thus, Applicant's last argument is not probative here.

As to Applicant's first argument, it is respectfully pointed out that the issue is not whether one can readily identify whether a deletion(s) is made, but rather, whether a particular deletion, or a deletion in some defined *portion*, will predictably correlate to the requisite function of proliferation activity. Therefore, once again Applicant's assertion is not probative here.

As to Applicant's remaining assertion, it may be true that every potential species or permutation need not be described. However, to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("The description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious" and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966. In instant case, Applicant describes a single species comprising a fusion protein where a portion of the G-CSFR extracellular domain is deleted. Therefore, the disclosure does not describe additional fusion proteins where there are deletions. In sharp contrast, the genus encompasses thousands of possibilities, with no clear guidance in the disclosure or in the art, as to any common feature or characteristic that will correspond to proliferation activity, irrespective of the location, combination or number of deletion(s).

Generally, the DNA structural features of either cytokine receptors or hormone ligand-binding domains (HBD) are not common to the members of the genus of claimed fusion molecules with respect to deletions in any portion of the G-CSFR. Each protein is encoded by a distinct DNA structure without any evidence to demonstrate interchangeability from one species to the next, with respect to proliferation activity. Furthermore, regarding G-CSFR there is considerable variability across species. (e.g., Fukunaga et al. PNAS, 1990; 87:8702-06; teaching that human and mouse G-CSF receptor cDNA comprised 62.5% homology).

The distinguishing characteristics for the claimed G-CSFR extracellular domain-deletion proteins are not sufficiently described in the instant disclosure, nor are such fusion structures provided for by knowledge in the art. First, it cannot be asserted that receptor families are well characterized in regard to their requisite functionality, based on the basis for classifications in the art. Indeed, with respect to deletions anywhere within the G-CSFR extracellular domain, **deletions would affect the very sequence motifs upon which receptor families are classified** (e.g., conserved Trp-Ser-X-Trp-Ser or WSXWS extracellular motif in Type-1 family). In other words, one cannot assert the shared organizational structure as support for filling the description gap, where sequence(s) in the very region comprising shared structural motifs are deleted.

For example, while certain sequence motifs are conserved amongst a group or family of cytokine receptors, each block of conserved sequence is separated by variable linker regions, where **deletions of even a single residue can affect folding**, which in turn will affect secondary and tertiary structure, which will further affect functionality in relation to a fusion protein. (e.g., Bazan, J.F. Proc. Natl. Acad. Sci. 1990; 87:6934-38, page, 6936, Figure 1; depicting sequence/structure alignment for several cytokine receptors).

Therefore a review of the literature is not sufficient to distinguish cytokine receptors with respect to predictable or interchangeable functionality in relation to fusion proteins, wherein any portion of the G-CSFR is deleted. The literature teaches that there are distinguishable sequence and structural characteristics amongst the various cytokine receptors families. Notably, "each cytokine also exhibits some specific activities ...[whereby]... the ability of a cell to respond to each of these [cytokine factor] factors specifically appears to be regulated by the specific expression of distinct receptor chains". (Taga et al. FASEB J. 1993; 7:3387-96; p. 3391, last ¶ bridging to p. 3392). It remains unclear how such variance can be translated into interchangeability for *any* deletion of *any* portion of a G-CSFR comprised in a fusion molecule. The prior art merely teaches that cytokine receptors within certain families, which comprise some shared combination of conserved sequence motifs, function similarly to bind their cognate cytokines. However, the issue is not whether the structural organizational similarities are predictive for a given cytokine receptor to function to bind a cognate cytokine in a cell, but whether a fusion protein will function predictably where any portion of the G-CSFR is deleted.

In sum, for the reasons of record and in the foregoing, it must be deemed that a sufficient number of nucleic acid structures encoding the fusion proteins of the invention have not been disclosed, regarding the genus of fusion molecules comprising deletions in any portion of the G-CSFR extracellular domain nor is such a lack of disclosure supplemented for in the prior art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. **Claims 5-6, 8, 10, 12, 15, 17 and 19-24 rejected under 35 U.S.C. 102(e) as being anticipated by Capon et al. (US 5,838,544; reference of record).**

This rejection is of record and repeated herein in salient part. A response to Applicants' arguments is set forth immediately following the body of this rejection which was made previously and is repeated herein.

The '544 patent teaches a chimeric constructs encoding a ligand-binding domain and a proliferation signaling domain (PSD), as well as vectors and cells containing said constructs. (e.g. Abstract; columns 22-25, Example 1; describing construction of various fusion proteins). The chimeric constructs also encode transmembrane domains (i.e., exogenous genes). (e.g., col. Figure 1). Alternatively, the nucleic acid constructs encoding the fusion proteins are mobilized into pBLUESCRIPT® vector backbone which comprises antibiotic selective genes exogenous gene) for maintenance and selection of the plasmids (e.g., in bacterial propagation). (e.g., col. 23, l. 22).

In addition, the chimeric construct can comprise an inducer-responsive clustering domain (ICD), i.e. hormone receptor domain, which upon binding the inducer or ligand will dimerize or cluster. (e.g. col. 3, ll. 33-39; See also, Fig. 1). Furthermore, the ICD domains can be eukaryotic steroid receptor molecules, including estrogen, progesterone, androgen, for example. (e.g. col. 14, last ¶). In addition, the PSD portion of the chimeric construct can be the transducing domains (i.e. proliferation domains) of the cytokine receptors, including IL-2 for example. (e.g. col. 16, last ¶ bridging to col. 17, ll. 1-19). Further, the PSD can be G-CSF. (e.g. col. 9, l. 54).

With respect to the limitation "vector system", the reference teaches multiple vectors (cols. 22-36, Examples 1-8). Furthermore, human 293 cells are transfected with various vector constructs. (e.g., col. 39, Example 10).

In addition, with respect to deletions of the G-CSFR, the reference teaches that certain amino acid sequences, of the gene(s) comprising the fusion protein, may in some instances be deleted, usually not more than 20 or 30 amino acids. (e.g., col. 14, ll. 11-27). More particularly the deletions can occur at the ends of the gene (e.g., N- or C-terminus of the extracellular domain). (e.g., col. 14, l. 11). Therefore, the reference anticipates the rejected claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that Capon's broad disclosure of a genus of chimeric receptor proteins, composed of any number of distinct domains at best describes a genus and does not explicitly teach the species to which the claims are directed. (Remarks, p. 16, ¶ 1). Further, Applicant asserts said species can only be anticipated only *if* one of ordinary skill in the art can "at once envisage" the species of the claimed invention. (Id.).

First, it is noted that Applicant acknowledges that Capon teaches a fusion molecule where at least two domains (ligand binding and proliferation domain) comprise said fusion molecules. (e.g., Remarks, p. 16, ¶ 2). Further, contrary to Applicant's assertion, Capon does explicitly signal to the artisan that the first domain can be selected from a certain list of specific molecules and that the second domain can be selected from a list of specific compounds. All that is required for one to envisage a species is that the specification must clearly point out to those skilled in art that the inventor is in possession of genus disclosed. Or as Applicant notes "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every species. (Remarks, p. 12, bottom, *citing*, *In re Grimme*, 274 F.2d 949, 952 (CCPA 1960).

In any event, one of ordinary skill can readily envisage the potential fusion molecules comprising at least two domains, where each domain is explicitly defined in the disclosure. (*See*, Non-Final Office Action, mailed 04 May 2005, at p. 17, outlining in detail Capon's teachings with respect to proliferation domains of G-CSF and ligand binding domains, which together comprise a fusion molecule). In view of the foregoing, Capon's teachings is deemed sufficient to envisage a fusion construct encoding a fusion protein comprising ligand binding domain of a steroid hormone and a proliferation domain of G-CSF. Thus the rejection is maintained.

Conclusion

Claims 14 and 18 appear to be free of the art thus are allowed. Claims 5-6, 8, 10, 12, 15, 17 and 19-24 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DAVID GUZO
PRIMARY EXAMINER